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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/485,943	06/07/95	FRIEDMAN J	600-1-[illegible]

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EXAMINER	
BAILEY, J	

ART UNIT	PAPER NUMBER
1636	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No. 08/485,943	Applicant(s) Friedman et al.
	Examiner J. Railey	Group Art Unit 1636

☒ Responsive to communication(s) filed on *27 Nov and 22 Dec 1998; 25 Jan 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *54-164* is/are pending in the application.

Of the above, claim(s) *54-123 and 125-131* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *124 and 132-164* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Claims 54-164 are pending. This office action is in response to papers filed 27 November 1998, paper No. 19; 22 December 1998, paper No. 20; and 25 January 1999, paper No. 21. The substitute specification filed 25 January 1999, which incorporates the changes of the Amendment supplied therewith, has been entered. The claims submitted with the substitute specification have not been entered, as those were canceled with applicant's amendment of 18 June 1997, paper No. 11.

Claims 54-123 and 125-131 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 11.

Claims 124 and 132-164 are examined hereinbelow.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124 and 132-164 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a gene encoding the OB polypeptide as shown in SEQ ID NOs: 2, 4, 5 or 6 as well as any OB polypeptide thereof lacking the signal sequence of amino acids 1-21, for modulating the body weight of *ob/ob* mice or normal mice, does not reasonably provide enablement for using other variants (except natural alleles), analogs and fragments of these OB polypeptides, nor is the specification enabling for modulating the body

weight of any other mammals, including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained essentially for reasons as set forth in the previous office action, paper No. 13, mailed 24 September 1997 and paper No. 17, mailed 21 May 1998.

Applicant's arguments filed 27 November 1998, paper No. 19, have been fully considered but they are not persuasive. Applicant first addresses the grounds of the rejection based upon the fact that the specification fails to enable other variants, analogs or fragments of the OB gene to function as claimed. Applicant's response at page 11 notes that they have removed the term "muteins" from the claims, but also acknowledges that they consider the term commensurate with the term "analog." Effectively, then, applicants have not really made an effort to "expedite issuance" of the instant application as a patent in this regard. Applicant presents no new arguments in support of these broad claims. Applicant is invited to review the grounds of the rejection as set forth in the last office action, paper No. 17 and note that there is a difference between naturally occurring alleles which possess **all** of the identifying characteristics of an OB gene and its encoded protein. Applicant's claims embrace an undeterminable number of unspecified "analogs" or fragments which ***might*** have ***some*** of the characteristics of the OB gene and its encoded protein. Applicant's comments regarding specific cites which are indicated as potentially mutable within the OB protein are not found persuasive as a "representative number"

of "analogs" for this protein. The reason is that applicant has clearly indicated that these 22 cites [sic, sites] were clearly demonstrable of species differences in the OB protein which ***do not*** affect the characteristics of the OB protein in its ability to affect weight in an *ob/ob* mouse. The skilled artisan could easily be directed to make specific amino acid changes within any or all of these specific sites and reasonably expect to obtain an protein which would be identifiable both structurally and functionally as an OB protein. In fact, it could be argued that applicant has set forth a comparison of the mouse and human genes and identified the specific sites where specific amino acids may differ, thus demonstrating a "generic mammalian OB protein" which is constant over the 83% of the amino acids found at specific sites. The other remaining sites could vary without affecting the identity of the OB protein. However, the terms "analog" or "variant" or "fragment" embrace a far more potential number of ***unidentified and unspecified*** changes to the OB protein than are supported by applicants alleged "representative number." Applicant provides ***absolutely no guidance*** to the skilled artisan on how or where the breadth of such changes are to be effected to arrive at the claimed invention, outside of the specific amino acid positions identified as variable through the comparison of the mouse and human proteins.

Applicant's comments on page 12 of the response regarding the second issue of enablement are also found unpersuasive. The examiner expended great effort in providing sound scientific reasoning in support of his position, a position augmented by references from the art. Applicant presents no substantive arguments or evidence in rebuttal, but rather presents an unsupported

conclusion. Again applicant is requested to review the grounds of the rejection presented in the last office action on identifying and selecting the population of individuals who would benefit from the treatment.

Claims 161 and 162 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained essentially for reasons as set forth in the previous office action, paper No. 17, mailed 21 May 1998.

Applicant's arguments filed 27 November 1998, paper No. 19, have been fully considered but they are not persuasive. Applicant argues that the skilled artisan could insert an expression regulatory control sequence in functional proximity to OB polypeptide encoding sequences. Again, these are simply unsupported statements of conclusion. Even if the skilled artisan might insert such control regions "immediately upstream and adjacent to the initiation methionine by homologous recombination," this does not take into account the fact that the native control sequences would still be present upstream of the gene present in the chromosome. What effect such native control sequences might still have over expression of the OB protein are unclear. A review of the reference by Gong et al. [The J. Biol. Chem. **271(8):**3971-3974 (1996)] shows the genomic structure and promoter analysis of the human OB gene. As shown in Figure 2, the gene is comprised of a complex promoter region with binding sites for several regulatory elements.

Applicant neither discloses such promoter structure nor predicts how these elements affect OB gene expression. In fact, applicant's specification does not even predict the existence of the three exon structure of the gene as shown by Gong et al., and this structure may even constitute an important level of regulation of gene expression. Claims 161 and 162 assume that it is simply routine in the art to insert an "expression regulatory sequence in functional proximity to the OB polypeptide encoding sequence" and expect that the OB gene will be activated. This would not have been enabled given the insufficient disclosure of the specification and the later teachings that the promoter region is likely regulated by a variety of "regulatory elements." Applicant does not teach the nature of why a particular OB gene might not be expressed, and therefore cannot propose how this expression would be corrected or enhanced through homologous recombinational events. For instance, an active repressor sequence could be present in one of the introns resulting in a down-regulation of OB mRNA translation. Simply altering a promoter region would not affect this down-regulation. In this regard, it is unclear where the skilled artisan might place an "expression regulatory sequence" such that it is in proper "functional proximity" to the coding sequence in this regard to function as claimed. Therefore, it cannot be said that simply inserting a new control region immediately upstream of the initiation methionine codon would automatically result in expression of the chromosomally located OB gene. Applicant fails to teach how such modifications would be accomplished, but begs the skilled artisan to experiment to try and enable the invention as claimed. This experimentation is considered prophetic and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 133, 141, 147, 157, and 164 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 133, 141, 147 and 157, the specification fails to set forth the meaning of the term "amino acid sequence identity" as claimed and how applicant arrived at this identity. This rejection is maintained for reasons as given in the previous office action, paper No. 17, mailed 21 May 1998.

Applicant's arguments filed 27 November 1998, paper No. 19, have been fully considered but they are not persuasive. Applicant argues that they have amended the claims to remove the term "homology" from the claims. However, the term "identity" is likewise vague and indefinite for reasons of record. The term identity means "the same." However, if two amino acid sequences are less than 100% identical, it is unclear where they differ unless it is clearly indicated where and how. The terms "homology," "similarity," or "identity" are vague and indefinite. This is because when two molecules are less than 100% homologous, similar or identical and no specific algorithm is set forth to define the terms, it cannot be determined what these terms exactly mean. The previous office action clearly indicated to applicant that a particular amino acid sequence may differ, or vary from a disclosed SEQ ID NO. at **very specific positions**. Applicant

should draft claims which clearly indicate exactly where the broadly claimed amino acid sequence differs by referring to specific SEQ ID NOs. and specific positions within those SEQ ID NOs. Otherwise, the claims remain vague and indefinite as to where two given molecules have "identity" and where they do not.

Regarding claim 164, the specification fails to teach what is a "moderate stringency hybridization condition." See page 47, first paragraph.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Art Unit 1636 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette,

1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1636 is (703) 308-4242 or 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. F. Railey, whose telephone number is (703) 308-0281. The examiner can normally be reached on Monday-Thursday, and alternate Fridays, from 8:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax phone number for informal transmissions to the examiner is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

2 April 1999

JOHNNY F. RAILEY II, PH.D.
PRIMARY EXAMINER
TECHNOLOGY CENTER 1600